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Microcontainers - an oral drug delivery system for poorly soluble drugs

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PURPOSE: To fabricate microcontainers in either SU-8 or biodegradable poly-L-lactic acid (PLLA), and fill the microcontainers with poorly soluble drugs. Furthermore, the application of the microcontainers as an oral drug delivery system was investigated in terms of release, *in situ* intestinal perfusion and oral bioavailability.

METHODS: SU-8 microcontainers were fabricated using lithography, whereas PLLA microcontainers were prepared by hot embossing. In terms of drug filling, the SU-8 microcontainers were filled with polyvinylpyrrolidone (PVP) by inkjet printing followed by supercritical CO₂ impregnation of ketoprofen into the PVP matrix. As an alternative filling method, the powder of amorphous sodium salt of furosemide, (ASSF) was filled into the SU-8 microcontainers. The PLLA microcontainers were filled with drug formulation by embossing the microcontainers into a polycaprolactone (PCL) and furosemide (4:1 w/w) layer. For the ASSF-filled microcontainers, an enteric-resistant lid of Eudragit L100 was spray coated onto the cavity of the microcontainers. Release of ASSF from the coated microcontainers was investigated using a μ -Diss profiler in simulated intestinal medium at pH 6.5. *In situ* intestinal perfusions were performed in rats of the Eudragit-coated ASSF-filled microcontainers and compared to a furosemide solution. The microcontainers were dosed to the small intestine, and at the end of the study, the small intestine was harvested from the rat and imaged under a light microscope. For the *in vivo* studies, the rats were dosed orally with capsules containing ASSF-filled microcontainers coated with Eudragit L100. As control, capsules were filled with the powder of ASSF and the capsules were coated with Eudragit L100.

RESULTS: The SU-8 microcontainers had an inner diameter of 220 μ m and a cavity depth of 270 μ m, and for the PLLA microcontainers the inner diameter was found to be 240 μ m and with a cavity depth of 65 μ m (Figure 1). The microcontainers were successfully filled with either PVP:ketoprofen, ASSF or PCL:furosemide. A fast release of ASSF from the microcontainers was observed and the Eudragit coating was shown not to be a hindrance for rapid release at intestinal conditions. For the intestinal perfusion studies, the absorption rate constant of ASSF was 1.5 fold higher, when ASSF was confined in the microcontainers compared to a furosemide solution. Micrographs of the small intestine after the perfusion studies showed that the microcontainers interact with the mucus in the small intestine, and the microcontainers are engulfed by the intestinal mucus. The oral bioavailability study showed that the relative oral bioavailability of ASSF in microcontainers is 220 \pm 43% when compared to drug-filled capsules coated with Eudragit. This is reflected by a larger area below the curve for the ASSF in microcontainers (Figure 2).

CONCLUSIONS: Both SU-8 and biodegradable PLLA microcontainers were successfully fabricated and loaded with poorly soluble drugs. A fast release of ASSF was facilitated from the SU-8 microcontainers.

Furthermore, the microcontainers were found to interact with the intestinal mucus resulting in a higher oral bioavailability when compared to non-confined ASSF. The fabricated microcontainers therefore show considerable future potential as oral drug delivery systems.

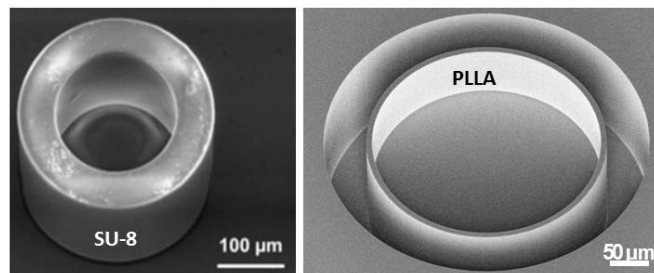


Figure 1: SEM images of SU-8 (left) and PLLA (right) microcontainers

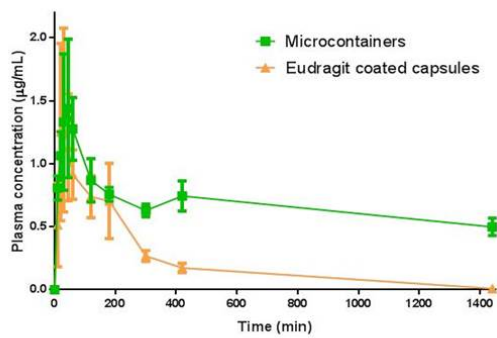


Figure 2: Plasma concentrations of microcontainers filled with ASSF coated with Eudragit L100 and filled into capsules and ASSF dosed in capsules with Eudragit coating after orally dosing to rats